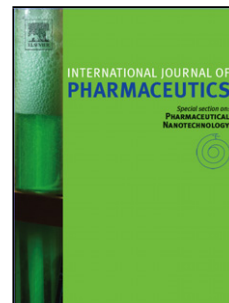


## Accepted Manuscript

Title: A Multifunctional  $\beta$ -Cyclodextrin-Conjugate  
Photodelivering Nitric Oxide with Fluorescence Reporting

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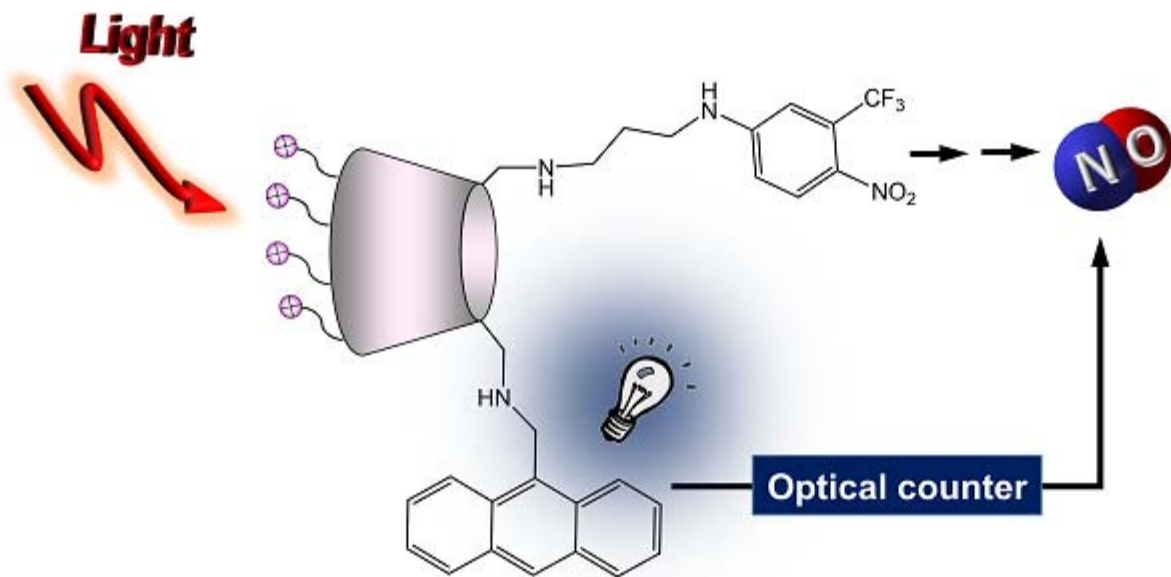
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*Special issue on Cyclodextrins***A Multifunctional  $\beta$ -Cyclodextrin-Conjugate Photodelivering Nitric Oxide with Fluorescence Reporting**

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**Abstract**

This contribution reports the design, synthesis and photochemical properties of a novel cationic, water soluble,  $\beta$ -cyclodextrin ( $\beta$ CD) conjugate integrating an anthracene moiety and a nitroaniline derivative within the primary side of the  $\beta$ CD scaffold. Photoinduced energy transfer between the anthracene and the nitroaniline chromophores effectively suppresses the fluorescence of the anthracene unit. Excitation with visible light triggers the release of nitric oxide (NO) from the nitroaniline chromophore, accompanied to the concomitant revival of the anthracene fluorescence, which acts as an optical reporter for detecting the amount of the NO released. Furthermore, the anthracene moiety photogenerates singlet oxygen ( $^1\text{O}_2$ ) sequentially to NO release. The conjugate is also able to accommodate hydrophobic guests within the  $\beta$ CD cavity, as proven by using naphthalene as a model compound. In view of the key role NO and  $^1\text{O}_2$  play as anticancer and antibacterial species, the present

$\beta$ CD derivative represents an intriguing candidate for further studies in biopharmaceutical research addressed to multimodal therapeutic applications.

**Keywords:** Cyclodextrin, nitric oxide, singlet oxygen, light, fluorescence,

## 1. Introduction

Cyclodextrins (CDs) have been greatly developed during the last thirty years as carriers of “conventional” drugs (Davis and Brewster, 2004; Loftsson and Douchene, 2007). However, the use of CDs as suitable vehicles for photoactivable therapeutic compounds has been only recently object of attention (Mazzaglia et al., 2012). Due to their hydrophobic cavity, natural CDs can host a variety of photosensitive agents by supramolecular interactions (Bortolus and Monti, 1996; Monti and Sortino, 2002). Nevertheless, in most cases, the low binding constants between unmodified CDs and guest molecules represent a major drawback of these systems as bio-carriers, making the modification of the CD structure strictly necessary in view of actual applications (Mazzaglia et al., 2006). Modification of the CDs molecular scaffold through functionalization of the primary and/or secondary hydroxyl groups with suitable photoresponsive units allows to obtain multifunctional nanocarriers with intriguing properties whilst, at the same time, maintaining the macrocycle’s capacity for guests encapsulation (Mourtzis et al., 2008; Mourtzis et al., 2007; Yannakopoulou et al., 2011).

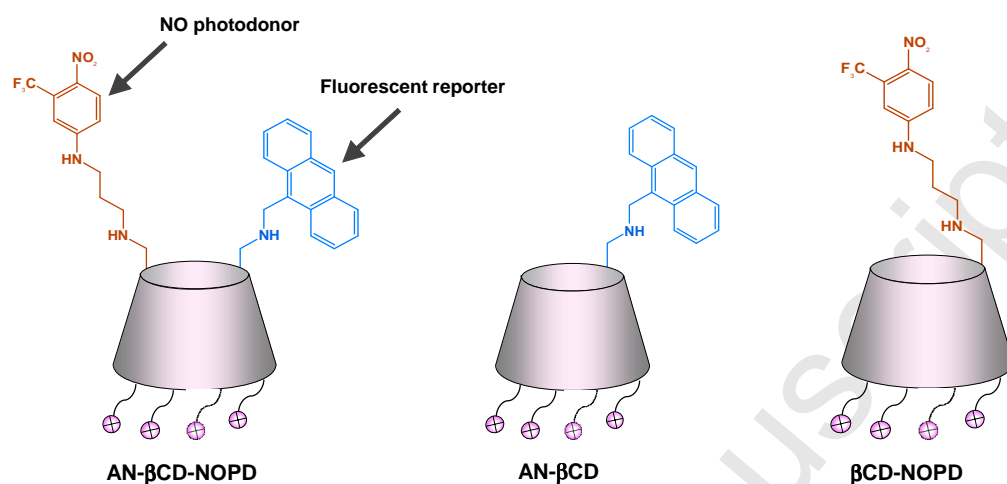
Nitric oxide (NO) is a pleiotropic bioregulator of important physiological and pathophysiological processes encompassing neurotransmission, vasodilatation and hormone secretion in living bodies (Ignarro, 2010). Besides, NO is an excellent sacrificial antioxidant, anticancer and antibacterial agent (Ignarro, 2009). This scenario has open a fervent research activity devoted to developing compounds able to release NO under physiological conditions as potential pharmaceuticals to fight a variety of

diseases (Wang et al., 2005; Wang et al., 2002; Riccio and Schoenfisch, 2012; Seabra and Durán, 2009). However, the biological effects of NO are strictly depending on its concentration, location and dose (Jia et al., 2002). This has made the light-activated NO donors very appealing due to the superb spatiotemporal accuracy the light triggering offers (Ford, 2008; Sortino, 2010; Fry and Mascharak, 2011; Ford, 2013). Several NO photodonors (NOPD) have been supramolecularly combined with CDs derivatives (Fraix et al., 2016). In contrast, only limited examples of NO photodonor covalent conjugates with CDs are reported to date (Piras et al., 2013).

Quantification of the NO delivery in real time is another important issue to be faced, especially when the main interest is to reach a critical molecule concentration to induce a specific effect. A suitable way to address this quantification task is based on the use of a *fluorescent reporter*. This elegant strategy relies on the simultaneous photorelease of the desired bioactive species, *i.e.* NO, and a fluorescent component (the reporter) from the same nonfluorescent precursor (Veldhuyzen et al., 2003; Pellois et al., 2004; Weinstein et al., 2010). The release process can be thus easily quantified by monitoring the fluorescence emission of the reporter, which acts exactly as an optical counter of the bioactive species. Recently, we have reported interesting properties of an *ad-hoc* designed molecular conjugate integrating two chromogenic centers within the same covalent skeleton (Vittorino et al., 2011; Kirejev et al., 2014), an anthracene moiety and a nitroaniline derivative, this latter as a suitable NOPD (28). In this compound, the typical emission of the anthracene fluorophore is completely suppressed by a photoinduced energy transfer to the nitroaniline moiety. We demonstrated that the photorelease of NO leads to the revival of the fluorescence of anthracene fluorophore which acts as a *fluorescent reporter* for the NO delivery in living cells (Vittorino et al., 2011; Kirejev et al., 2014).

Based on the above scenario we considered it of value to translate this NO photorelease with fluorescent reporting concept in a novel conjugate, which covalently integrates the NO photoreleaser and the anthracene moiety within the same positively charged  $\beta$ CD scaffold. This contribution reports

the synthesis, characterization and photochemical properties of the cationic  $\beta$ CD conjugate **AN- $\beta$ CD-NOPD** and the suitable model compounds **AN- $\beta$ CD** and  **$\beta$ CD-NOPD** (Fig. 1).



**Fig 1.** Schematic of the multifunctional  $\beta$ -CD conjugate **AN- $\beta$ CD-NOPD** and the model compounds **AN- $\beta$ CD** and  **$\beta$ CD-NOPD**.

## 2. Experimental section

### 2.1. Chemicals

6-Monodeoxy-6-monoazido- $\beta$ CD and 6-monotosyl- $\beta$ CD are fine chemical products of CycloLab, 1,3-diaminopropanol ( $\geq 99\%$ ), 4-nitro-3-(trifluoromethyl)aniline (98%), glycidyltrimethylammonium chloride (technical grade,  $\geq 90\%$ ), sodium azide (ReagentPlus®,  $\geq 99.5\%$ ), hydrazine monohydrate (reagent grade, 98%), sodium borohydride ( $\geq 98.0\%$ ), anthracene-9-carboxaldehyde ( $\geq 97.0\%$ ), p-toluenesulfonyl chloride (ReagentPlus®,  $\geq 99\%$ ), trimethylamine ( $\geq 99\%$ ), 1,3-propanedithiol ( $\geq 99\%$ ), palladium on carbon (5%), were sourced from Sigma-Aldrich.

Dimethyl sulfoxide, formic acid, methanol, pyridine were obtained from Molar Chemicals.

## 2.2. Instrumentation

$^1\text{H}$ -,  $^{13}\text{C}$ - NMR spectra and DEPT-ed-HSQC spectra were recorded in DMSO- $\text{d}_6$  or  $\text{D}_2\text{O}$  (10 mg dissolved in 0.8 mL of deuterated solvent) on a Varian DDR-600 at 600 MHz spectrometer at 298 K.

Mass spectra were obtained on Bruker ESQUIRE 3000 ES-ion trap instrument with electrospray ionization (ESI) in negative mode. All samples were dissolved in water.

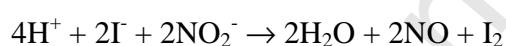
Preparative chromatographic separations were performed on a Büchi preparative chromatography system using SiliCycle Silica Cartridge (4 cm x 15 cm) packed with Lichroprep (120 g) RP-18 Phase (40-63  $\mu\text{m}$ ) as a stationary phase and water-methanol gradient elution. The chromatographic station was equipped with Büchi UV Photometer C-635 as a detector (detection wavelength set at 390 nm for NOPD appended derivatives and at 245 nm for the tosylated intermediate).

UV-Vis absorption and fluorescence spectra were recorded with a Jasco V 650 spectrophotometer and a Fluorolog-2 (Model, F111) spectrofluorimeter, respectively. Fluorescence lifetimes were recorded with the same spectrofluorimeter equipped with a TCSPC Triple Illuminator. The samples were irradiated by a pulsed diode excitation source Nanoled at 370 nm. The kinetic was monitored at 420 nm and each solution itself was used to register the prompt at 370 nm. The system allowed measurement of fluorescence lifetimes from 200 ps. The multiexponential fit of the fluorescence decay was obtained using the following equations:  $I(t) = A_1\exp(-t/\tau_1) + A_2\exp(-t/\tau_2)$  (for the biexponential fit) and  $I(t) = A_1\exp(-t/\tau_1) + A_2\exp(-t/\tau_2) + A_3\exp(-t/\tau_3)$  (for the triexponential fit). Multiexponential fitting were used because they gave much better chi-square values than monoexponential fitting.

$^1\text{O}_2$  emission was registered with the same spectrofluorimeter as above equipped with a NIR-sensitive liquid nitrogen cooled photomultiplier, exciting the air-equilibrated samples in  $\text{D}_2\text{O}$  solution at 380 nm with the fluorimeter lamp.

Photolysis of the samples in solution was performed in a thermostated quartz cell (1 cm pathlength, 3 mL capacity) under gentle stirring, by using a continuum laser with  $\lambda_{\text{exc}} = 405$  nm (ca. 100 mW) having a beam diameter of ca. 1.5 mm.

NO release was measured with a World Precision Instrument, ISO-NO meter, equipped with a data acquisition system, and based on direct amperometric detection of NO with short response time ( $< 5$  s) and sensitivity range 1 nM – 20  $\mu$ M. The analog signal was digitalized with a four-channel recording system and transferred to a PC. The sensor was accurately calibrated by mixing standard solutions of NaNO<sub>2</sub> with 0.1 M H<sub>2</sub>SO<sub>4</sub> and 0.1 M KI according to the reaction:



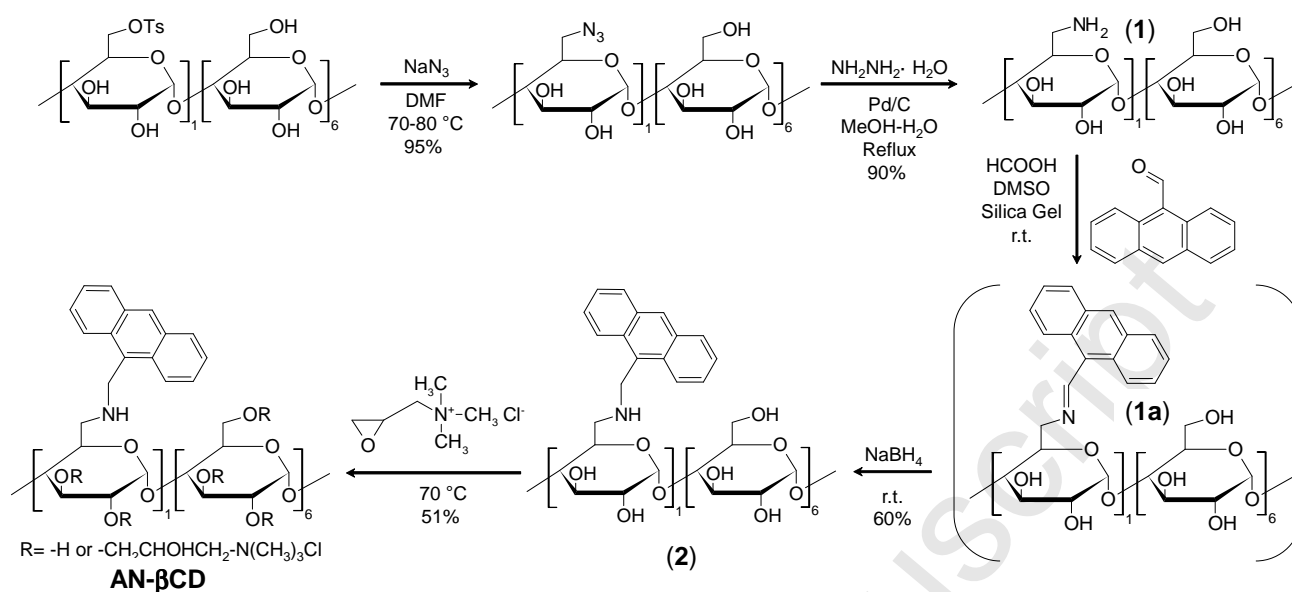
Irradiation was performed in a thermostated quartz cell (1 cm path length, 3 mL capacity) under gentle stirring by using the same 405 nm laser sources described above. NO measurements were carried out with the electrode positioned outside the light path in order to avoid false NO signal due to photoelectric interference on the ISO-NO electrode

### 3. Results and discussion

#### 3.1 Syntheses

The model compound **AN- $\beta$ CD** was synthesized according to the procedure illustrated in Scheme 1 and briefly described in the following (the full details are reported in the Supporting Information).



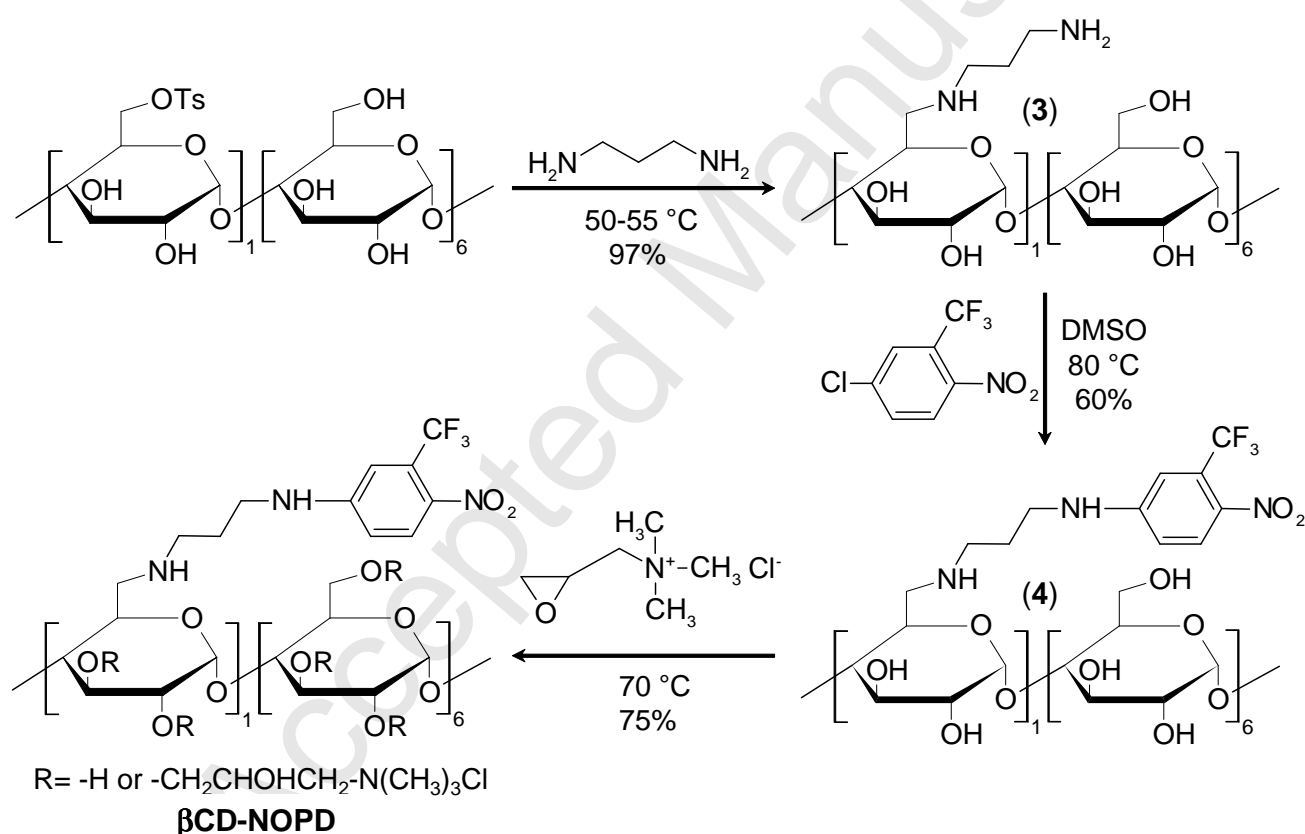


**Scheme 1.** Reaction scheme for the synthesis of AN-βCD.

6-monotosyl-βCD was promptly converted to the amino-analogue **1** by exhaustive reduction of the intermediate 6-monodeoxy-6-monoazido βCD, according to literature (Jicsinszky and Iványi, 2001). The amino group, located on the primary rim of CD scaffold, is a suitable anchoring point for the introduction of the anthracene chromophore. As compound **1** is obtained as free base, the coupling could be achieved by a nucleophilic substitution in DMF with the commercially available 9-(chloromethyl)anthracene. This reaction setting was explored, but the conversion rate was not satisfactory (~30% formation of compound **2**) and *N*-dialkylated product (CD scaffold containing two anthracene moieties) was considerably formed under the tested experimental conditions (~10%). Although chromatographic purification of the crude can be attempted, the procedure is time-consuming, not effective and resulted in low-yield. As efficient alternative for the preparation of compound (**2**) a two-steps one-pot reaction based on imine-reduction, allowing good conversion rate and avoiding chromatographic purification, was applied. The addition of silica gel to the reaction mixture during the first step was a fundamental requirement for achieving quantitative conversion to the imine intermediate **1a**. The nano-porous material was effective in removing the water accumulated

during the condensation process thus making convenient the coupling reaction. The second step based on the mild reducing agent sodium borohydride proceeded quantitatively within expectations. The introduction of the permanent charges on the CD scaffolds was achieved by using the alkylating agent, glycidyltrimethylammonium chloride, as reaction solvent. This approach has the advantages of minimizing the by-products formation and reducing the work-up to simple fractional crystallization cycles.

The model compound  **$\beta$ CD-NOPD** was synthesized according to the procedure illustrated in Scheme 2 and briefly described in the following (the full details are reported in the Supporting Information).



**Scheme 2.** Reaction scheme for the synthesis of  **$\beta$ CD-NOPD**.

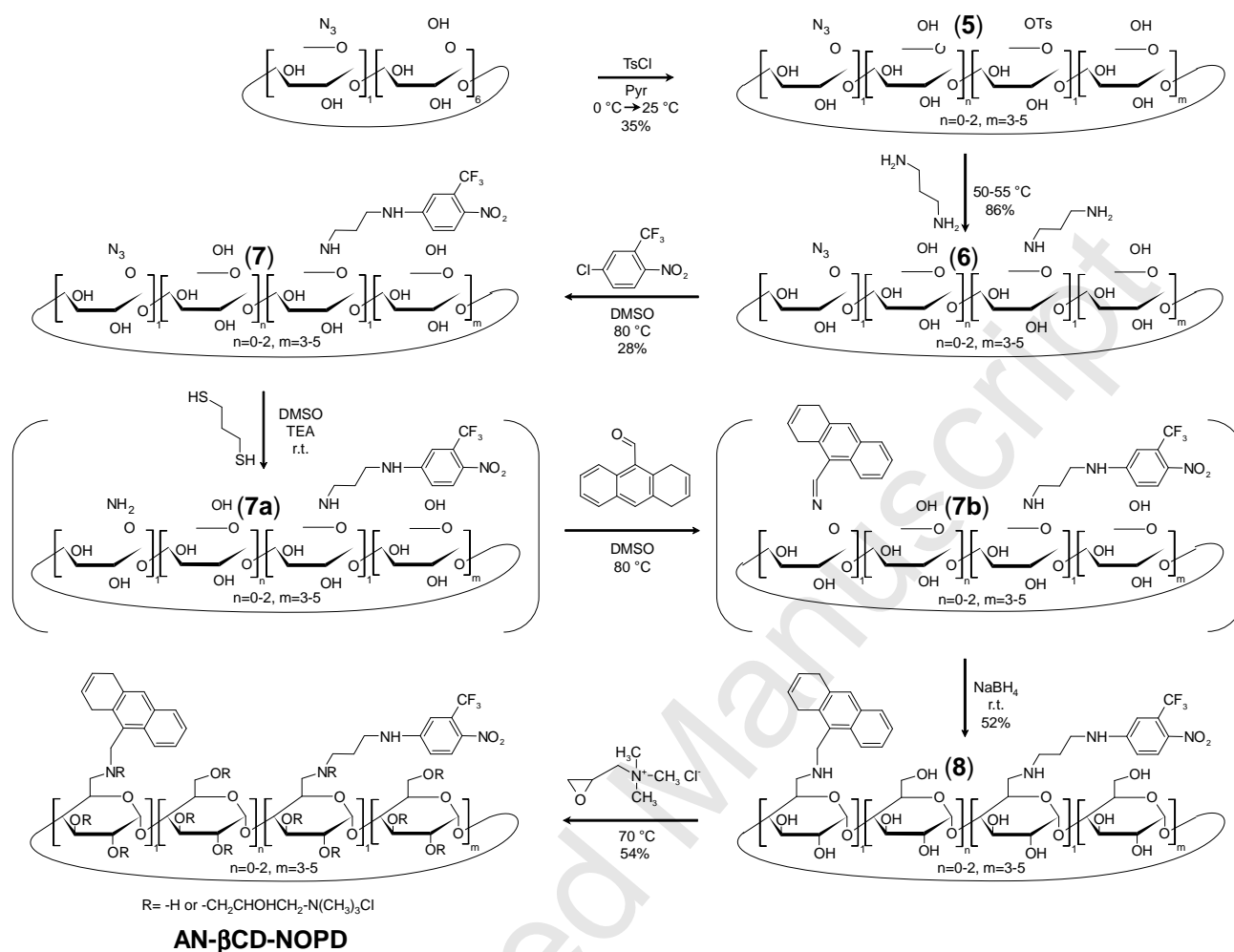
The flexible linker, 1,3-diaminopropane, was effectively introduced on the CD scaffold by nucleophilic substitution on the 6-monotosyl- $\beta$ CD. In order to reduce the formation of by-products such as CD

dimers (two or more CD units connected through the linker) and 3,6-anhydro derivatives, 1,3-diaminopropane was used in large excess (reaction solvent) and 6-monotosyl- $\beta$ CD was added portion-wise to the warm solvent solution. These precautions ensured that 6-monotosyl- $\beta$ CD was always acting as limiting reagent and promptly converted to 6-monodeoxy-6-mono-(3-aminopropylamino)  $\beta$ CD. The large excess of 1,3-diaminopropane in combination with an adequate work-up (evaporation under reduced pressure and precipitation with methanol-diisopropyl ether mixture) also maintained compound **3** in free base form. This is a strict requirement to successfully accomplish the following reaction step as no extra base can be added to the reaction mixture due to the high reactivity of 4-chloro-1-nitro-2-(trifluoromethyl)benzene towards these species. It is worth to mention that the decision of attaching the NOPD moiety to the CD scaffold through a linker, was the result of several unsuccessful attempts to directly introduce the chromophore on the CD rim. No adequate reaction conditions were found to react the reagent 4-chloro-1-nitro-2-(trifluoromethyl)benzene with the free base of 6-monoamino-6-monodeoxy- $\beta$ CD. The most probable reason is that the nitrobenzene derivative formed a strong inclusion complex with the  $\beta$ CD cavity locating the chlorine atom on the secondary side (Ueno and Breslow, 1982). The establishment of this supramolecular interaction precludes primary-side substitution.

Compound **4** was obtained in moderate yield by reacting the free base of compound **3** with 4-chloro-1-nitro-2-(trifluoromethyl)benzene. As no extra base could be added to the reaction mixture without consuming the chromophore, the product was formed only at around 40% conversion rate. Reversed-phase chromatographic purification was needed to separate the unreacted compound **3** from the target product. The solubility profile of compound **4** was improved by modifying some of the hydroxyl groups with permanently charged side-chains.

The multifunctional conjugate **AN- $\beta$ CD-NOPD** was synthesized according to the procedure illustrated in Scheme 3 and briefly described in the following (the full details are reported in the Supporting Information). In order to introduce both the chromophores on the primary side of the CD scaffold,

tosylation of 6-monoazido-6-monodeoxy- $\beta$ CD was performed in pyridine. This approach is selective for the modification of the primary rim of the macrocycle (Matsui et al., 1976) and generates a mixture of three pairs of pseudoenantiomers ( $6^A$ -monodeoxy- $6^A$ -monoazido- $6^X$ -monotosyl- $\beta$ -CD, compound **5**). The mixture of primary-side hetero-disubstituted  $\beta$ CD was isolated by preparative reversed-phase chromatography. The strategy developed for the introduction of the NOPD chromophore in model compound  **$\beta$ CD-NOPD** was applied at this stage almost without modifications. The azido moiety remained unaltered both in harsh alkaline conditions (preparation of compound **6**) and during the prolonged heating required for the nitrobenzene installation (preparation of compound **7**). The most challenging part of the synthetic work was the introduction of the anthracene fluorophore on the NOPD-appended CD. A three-step one-pot reaction was carefully designed to fulfill all the necessary requirements. First, a mild reduction method was chosen for the selective reduction of azido group in the presence of the aromatic nitro group. This approach was based on the use of 1,3-propanedithiol and trimethylamine as reduction mixture to obtain the amino-intermediate **7a**. Addition of anthracene-9-carboxaldehyde and heating of the reaction mixture resulted in almost complete conversion (90% conversion rate based on TLC estimation) to anthracene-appended imine-intermediate **7b**. Portion-wise addition of  $\text{NaBH}_4$  and prolonged stirring at room temperature afforded anthracene-appended amine-intermediate, compound **8**, in quantitative conversion. Preparative reversed-phase chromatographic purification allowed the removal of the unreacted compound **7a** and the isolation of targeted compound **8**. As the CD scaffold is modified simultaneously with two aromatic units, its solubility in aqueous environment is limited. This drawback was overcome by introducing quaternary ammonium bearing moieties in the system, obtaining the desired compound **AN- $\beta$ CD-NOPD**.

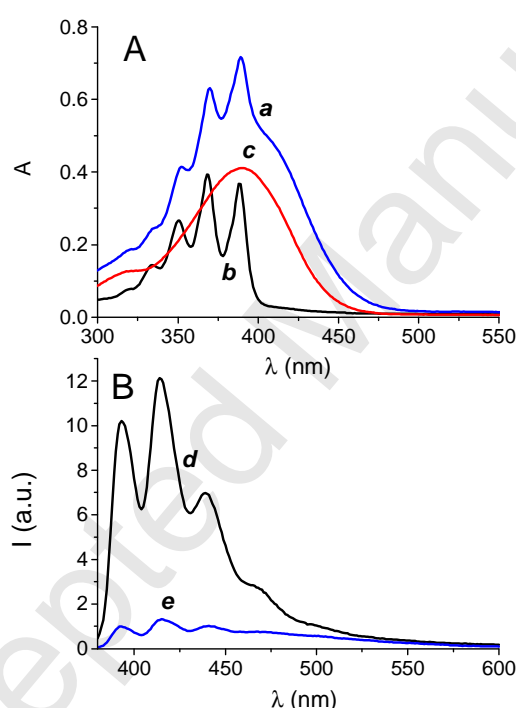


**Scheme 3.** Reaction scheme for the synthesis of AN-βCD-NOPD.

### 3.2 Spectroscopic properties and photochemical behavior

All compounds synthesized are well soluble in aqueous medium due to the presence of the cationic termination mainly located at the secondary rim of the βCD scaffold. The absorption spectrum of AN-βCD-NOPD (**a** in Fig. 1A) exhibits the distinctive spectral features of the anthracene chromophore below 400 nm and an intense absorption at longer wavelengths extending beyond 450 nm, due to the contribution of the nitroaniline moiety. This spectrum reflects quite well the sum absorption spectrum of the independent model compound AN-βCD and βCD-NOPD (**b** and **c** in Fig. 2A.), ruling out any significant interaction between the anthracene and nitroaniline chromophores in the ground state. On

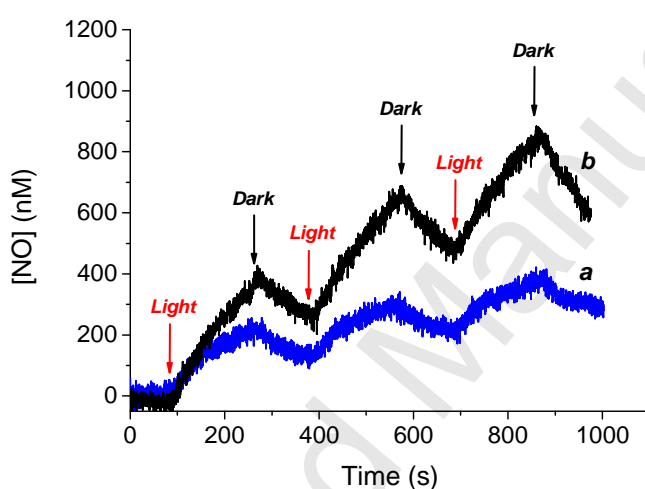
the other hand, the intense fluorescence emission of the anthracene fluorophore observed in the case of **AN- $\beta$ CD** (*d* in Fig. 2) is significantly quenched in the bichromophoric conjugate **AN- $\beta$ CD-NOPD** (*e* in Fig. 2B), suggesting a remarkable interaction between the two chromophores in the excited state. According to what already demonstrated in our previous studies (Vittorino et al., 2011; Kirejev et al., 2014), this drastic fluorescence quenching can be explained on the basis of a photoinduced energy transfer between the anthracene fluorophore and the nitroaniline components in the conjugate, which is encouraged by the close proximity of the donor and acceptor, both linked at the same rim.



**Fig 2.** (A) Absorption spectra of 40  $\mu$ M aqueous solution **AN- $\beta$ CD-NOPD** (*a*) and the model compounds **AN- $\beta$ CD** (*b*) and  **$\beta$ CD-NOPD** (*c*). (B) Fluorescence emission spectra ( $\lambda_{\text{exc}} = 370$  nm) of the model compound **AN- $\beta$ CD** (*d*) and **AN- $\beta$ CD-NOPD** (*e*).

The capability of **AN- $\beta$ CD-NOPD** to deliver NO under light stimuli was investigated by the direct and real-time monitoring of this transient species using an ultrasensitive NO electrode which directly reveals NO with nM concentration sensitivity by an amperometric technique (Coneski and

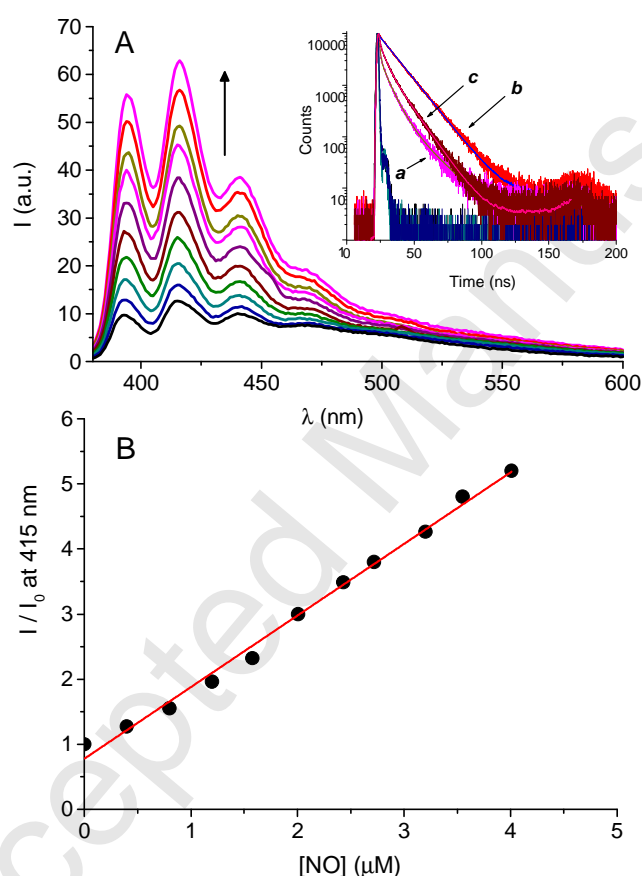
Schoenfisch, 2012). The absorption spectral features of **AN- $\beta$ CD-NOPD** allow the selective excitation of the NO photoreleaser component of the conjugate at  $\lambda_{\text{exc}} > 400$  nm. The results illustrated in Figure 3 provide unambiguous evidence that the bichromophoric CD conjugate is very stable in the dark but supplies NO upon illumination with  $\lambda_{\text{exc}} = 405$  nm. Note that, the rate of photorelease is very similar to that observed for an optically matched solution of the model compound  **$\beta$ CD-NOPD**.



**Fig 3.** NO release profile observed for optically matched aqueous solutions of **AN- $\beta$ CD-NOPD** (*a*) and  **$\beta$ CD-NOPD** (*b*) upon irradiation with  $\lambda_{\text{exc}} = 405$  nm at 25 °C.

NO photorelease from **AN- $\beta$ CD-NOPD** is accompanied by dramatic revival of the characteristic emission arising from the anthracene fluorophore. Fig. 4A shows the fluorescence emission spectra observed at regular irradiation times with visible light up to 45 min. This fluorescence restoring is due to the formation of a reaction product formed after the loss of NO that, in contrast to the nitroaniline derivative, is not a good energy acceptor and thus is not able to quench the fluorescence of the anthracene fluorophore. This behavior also reflects in the dynamic of the emission. As shown in the inset in Fig. 4A, the fluorescence decay of **AN- $\beta$ CD-NOPD** (trace *a*) was shorter than that of the model

compound **AN- $\beta$ CD** (trace *b*). However, after 45 min irradiation of the **AN- $\beta$ CD-NOPD** solution, the fluorescence dynamic become slower (trace *c*), according to the revival of the fluorescence. In such a way, the anthracene unit represents an excellent optical reporter for the NO release. In fact, as illustrated in Fig. 4B, we found an excellent linear correlation between the concentration of NO photogenerated and the increase of the fluorescence intensity of the optical reporter.

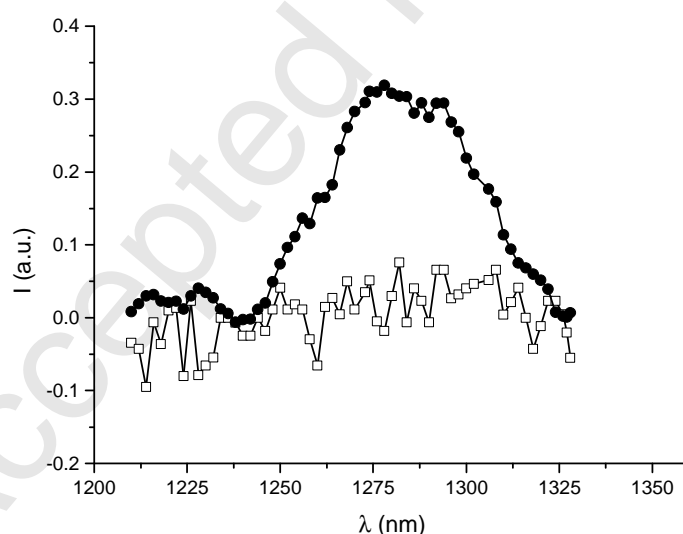


**Fig 4.** (A) Fluorescence ( $\lambda_{\text{exc}} = 370$  nm) spectral changes observed upon irradiation of an aqueous solution of **AN- $\beta$ CD-NOPD** ( $40 \mu\text{M}$ ) at regular irradiation times of 5 min (from bottom to top) with visible light ( $\lambda_{\text{exc}} = 405$  nm). The inset shows the fluorescence decay and the related multiexponential fitting for solutions of **AN- $\beta$ CD-NOPD** (*a*), the model compound **AN- $\beta$ CD** (*b*) and **AN- $\beta$ CD-NOPD** after 45 min irradiation with visible light (*c*);  $\lambda_{\text{exc}} = 370$  nm;  $\lambda_{\text{em}} = 420$  nm. (B) Correlation of the fluorescence increase observed in Fig. 4A and the concentration of NO released from the same solution



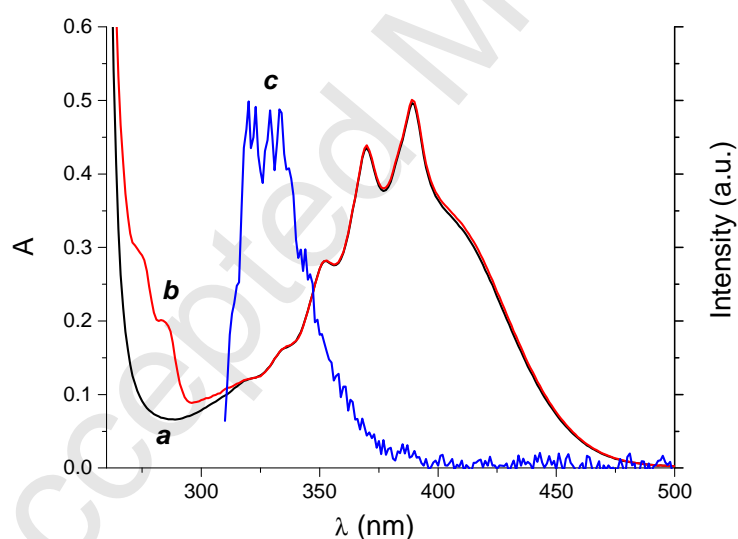
( $I$  and  $I_0$  represent the fluorescence intensities at 420 nm after each irradiation time and that of the non-irradiated solution, respectively).

Note that, the suppression of the quenching of the excited state of anthracene after NO release reflects also in the capability of this component to photosensitize the formation of singlet oxygen ( $^1\text{O}_2$ ), the key species in photodynamic therapy of cancer and bacterial diseases (Hasan et al., 2000). This was directly demonstrated by direct detection through monitoring of the typical phosphorescence of  $^1\text{O}_2$  in the near-IR spectral window (Wilkinson et al., 1993). Figure 5 shows that excitation of **AN- $\beta$ CD-NOPD** at  $\lambda_{\text{exc}} = 370$  nm does not lead to any detectable formation of  $^1\text{O}_2$ , according to effective quenching occurring of the anthracene by the nitroaniline component. On the other hand, excitation at the same wavelength after irradiating the **AN- $\beta$ CD-NOPD** solution for 1 h at 405 nm, leads to the appearance of the characteristic luminescence signals of  $^1\text{O}_2$  with maximum at *ca.* 1270 (Fig. 5).



**Fig 5.** Luminescence spectra detected upon 370 nm light excitation of a  $\text{D}_2\text{O}$  solutions of **AN- $\beta$ CD-NOPD** (40  $\mu\text{M}$ ) before ( $\square$ ) and after ( $\bullet$ ) 1 h irradiation at  $\lambda_{\text{exc}} = 405$  nm.

Despite the covalent linking with the two chromophores, the CD cavity of **AN- $\beta$ CD-NOPD** is still able to accommodate hydrophobic guests. This was proven by using naphthalene as a model compound, which is insoluble in water medium. To this end, a methanol solution of naphthalene was prepared. After drying the solvent, the resulting dried sample was added of an aqueous solution of **AN- $\beta$ CD-NOPD** and the sample was stirred for 1 h at room temperature. The mixture was then filtered and analysed by UV-Vis absorption. Fig. 6 shows the spectroscopic properties of **AN- $\beta$ CD-NOPD** before the addition to the film sample (**a**) and after the filtration procedure (**b**). The presence of the typical structured absorption bands of the naphthalene at ca. 275 and 285 nm (**b**) provides unambiguous evidence for the encapsulation of the guests within the CD cavity. Besides, the characteristic fluorescence emission of naphthalene (**c** in Fig 6) further confirms the effective formation of the host-guest supramolecular complex.



**Fig 6.** Absorption spectra of an aqueous solution of **AN- $\beta$ CD-NOPD** (30  $\mu$ M) (**a**) and its complex with naphthalene (**b**) (left Y-axis). Fluorescence emission spectrum (**c**) observed upon excitation at  $\lambda_{\text{exc}} = 280$  nm of the sample **b** (right Y-axis).

#### 4. Conclusions

We have devised and synthesized a novel multifunctional CD conjugate, bearing a nitroaniline and an anthracene chromophoric unit, able to incorporate a number of functionalities within the same molecular skeleton. **AN- $\beta$ CD-NOPD** is well soluble in water due to the cationic appendages present at the lower rim of the CD scaffold and is able to deliver NO under the exclusive control of visible light stimuli. NO photorelease restores the fluorescence of the anthracene fluorophore, which acts as an optical reporter of NO concentration. To the best of our knowledge, this represents the *first example* of NO photodispenser with fluorescence reporting integrated in a CD scaffold. Furthermore, we have demonstrated that the anthracene component is also capable to photogenerate  $^1\text{O}_2$  sequentially to the NO release. The **AN- $\beta$ CD-NOPD** conjugate is also able to accommodate hydrophobic guests within the  $\beta$ CD cavity, as proven by using naphthalene as a model compound. In view of the key role NO and  $^1\text{O}_2$  plays in photodynamic therapy, this  $\beta$ CD derivative represents an intriguing candidate for biopharmaceutical research. Studies in this direction are currently underway in our laboratories.

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